The SULSA Assay Development Fund

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The SULSA Assay Development Fund: accelerating translation of new biology from academia to pharma

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With industry increasingly sourcing preclinical drug discovery projects from academia it is important that new academic discoveries are enabled through translation with HTS-ready assays. However, many scientifically interesting, novel molecular targets lack associated high-quality, robust assays suitable for hit finding and development. To bridge this gap, the Scottish Universities Life Sciences Alliance (SULSA) established a fund to develop assays to meet quality criteria such as those of the European Lead Factory. A diverse project portfolio was quickly assembled, and a review of the learnings and successful outcomes showed this fund as a new highly cost-effective model for leveraging significant follow-on resources, training early-career scientists and establishing a culture of translational drug discovery in the academic community.

Introduction

Seismic changes are underway in the methods and organisational models used to discover modern medicines in response to the decline in productivity from traditional pharmaceutical industry approaches. Notable among these changes is the shift towards open innovation, which has promoted synergistic, collaborative programmes between different sectors including academia, biotech, charities, public institutes, CROs and major pharma companies. Major initiatives have been established to promote these collaborative approaches. For example, the EU commission and European Federation of Pharmaceutical Industries and Associations (EFPIA) have funded, through the €2 billion Innovative Medicines Initiative (IMI), the creation of the European Lead Factory (ELF), a collaborative public–private partnership delivering innovative drug discovery starting points backed with an investment of €196 million (http://www.europeanleadfactory.eu/) [1,2].

A key initial step for translational biology to succeed in delivering nascent medicines is the identification of high-quality chemical matter that predictably modulates a desired biological effect [3]. Multiple methods exist for generating or discovering lead compounds but all rely on access to one or more assays that are reproducible and have a capacity or throughput matched to the techniques being employed. The expertise and facilities required to create these high-throughput assays have traditionally resided in pharma companies and lack of access has limited the approaches employed by groups outside of industry. This is particularly evident for life science academics who rarely have the expertise or equipment to carry out HTS on the scale of $\geq$0.5 million compounds as conducted in large pharma or the ELF.

The pharmaceutical industry has thus been increasing its efforts to collaborate with universities and benefit from translational research in a bid to enhance innovation in early-stage drug discovery, essentially to bolster their shrinking drug pipelines and counteract the ongoing patent cliff. Over the past 10–15 years this has resulted in significant inward investment from pharma towards universities and a significant rise in the number of academic drug discovery groups [4–6]. University scientists have, to their advantage, witnessed a rise in industry-sponsored schemes aimed at screening novel targets and biological assays, and exploiting new

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BOX 1

European Lead Factory technical acceptance criteria

- Minimally 384 wells (max 30 μl)
- Homogenous assay (no washing steps)
- Defined endpoint
- *Z*-prime >0.6
- Readout stability >1 h
- S/B signal >3
- Incubation times <4 h
- DMSO tolerance: minimum 0.5%
- All reagents minimally 8 h stable
- Recombinant proteins(s) >80% pure

leads derived from their research [7]. However, to maintain these new initiatives, putative drug targets emerging from basic science first need to be enabled with HTS-ready assays and, as mentioned, developing such assays requires knowledge and experience, which many academic researchers will probably not have been exposed to. In particular, there is a need to understand acceptable experimental robustness criteria and comprehend the pitfalls and potential liabilities involved in screening [3,8]. This knowledge gap in the academic community was identified by the Scottish Universities Life Sciences Alliance (SULSA), which responded by establishing a pump-priming fund called the SULSA Assay Development Fund (SULSA-ADF) administered by the European Screening Centre (ESC) in Newhouse, Lanarkshire (http://www.lifesci.dundee.ac.uk/research/esc).

The aim of the SULSA-ADF was to source novel targets from the SULSA community and develop HTS-ready assays to a standard acceptable for submission to the ELF. The ELF is a European-wide initiative providing academics and small-medium enterprises (SMEs) access to large-scale HTS of proprietary industry-grade libraries [9,10]. However, to be eligible for screening in the ELF the target must come with an assay that meets a number of stringent quality control and logistical criteria (Box 1). Looking at these criteria, it is not hard to see that many academic labs struggle to meet them. For example, the very first specification: 'minimally 384-well', is a format not often used in university labs because HTS is not a primary consideration when acquiring equipment. Although the fund aimed to develop assays meeting the ELF criteria, assays developed to this level of robustness could also be eligible for a number of other industry-funded programmes such as Astra Zeneca's Open Innovation Portal, or GSK's Discovery Partnerships with Academia (DPAc). Submitting to these kinds of schemes was encouraged in the community to maximise the positive outcomes of the SULSA-ADF.

Scope, structure and aims of the SULSA-ADF

SULSA is a research pool that was established in 2008 with funds of £27 million from the Scottish Funding Council (SFC). It is a strategic collaboration between six member Scottish universities: Aberdeen, Dundee, Edinburgh, Glasgow, St. Andrews and Strathclyde. The aim of the pool is to enhance research excellence in the life sciences in Scotland, by joining up research strategy for larger projects and co-investing and sharing core research facilities. SULSA also has a remit to enhance translational research, which sparked the idea for a translational fund, and led to the creation of the SULSA-ADF in 2014, enabled with a modest investment of £300 000.

A competitive call for proposals was developed and widely advertised throughout Scotland to attract the best and most innovative academic projects with the aim of recruiting 18 projects to deliver 12 assays successfully developed to ELF standards. Project submissions are reviewed by a panel of four experts who use their extensive industrial and academic drug discovery experience to score the proposals. Proposals are accepted when there is a clear unmet medical need or they have the potential for delivering a novel therapy. They must also have a clear rationale for developing an HTS-compatible assay using established screening technologies (i.e. no blue-sky development of unprecedented assay concepts). Evidence for the availability of active reagents is also requested. Upon project acceptance, an initial teleconference between ESC scientists and the project owner (PO) is arranged to plan the assay development strategy, identify material requirements and set appropriate timelines.

The fund provides two expert ESC assay development scientists to industrialise the assay, as well as all commercially available consumables. Applicants are expected to provide any non-commercially available reagents such as recombinant proteins, bespoke substrates or proprietary cell lines. However, if required, they can directly access up to £3000 to help with protein production. The intention is to use the SULSA funding as efficiently as possible by developing assays rapidly, avoiding potentially open-ended development and trouble-shooting that can tie up resources and extend portfolio development timelines. A streamlined workflow (Fig. 1) has been designed so that, upon receipt of reagents, a 2-week feasibility assessment is undertaken for each assay. If a promising assay window cannot be established during this period then the assay is returned to the PO with recommendations on how to improve on the assay starting point. They are invited to resubmit the project with supporting data once they have successfully implemented the suggested improvements. For projects judged to have a

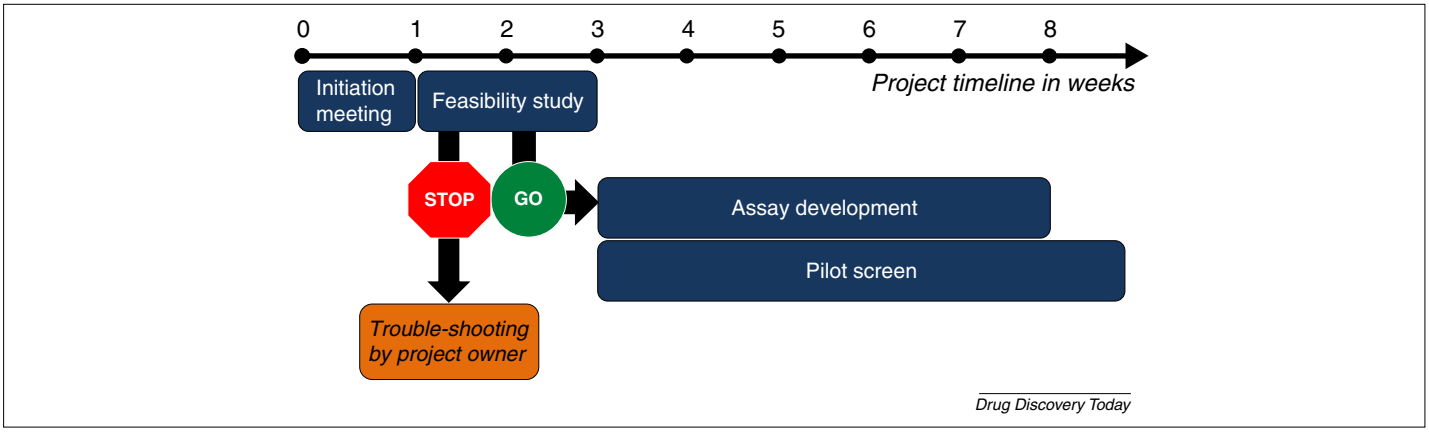

FIGURE 1

The SULSA Assay Development Fund workflow. Designed to ensure efficient use of resources and maximise project throughput.

TABLE 1

Project delivery goals and achievements of the SULSA-ADF

	Original goal	Achieved
Project recruitment	18	22
Assays developed to European Lead Factory (ELF) criteria	12	13
Projects submitted to ELF	10	7 (2 in preparation)
Projects accepted by ELF	6	5 (1 under review)

workable assay window, the assay is progressed with the aim of meeting the ELF assay technical criteria. The whole process from start to finish is intended to take no longer than 8 weeks per project on average. Although the primary deliverable for SULSA-ADF is a standard operating procedure (SOP) and associated data, a secondary aim is to run a small-scale pilot screen against ~7000 compounds. These compounds consist of the NIH Clinical Collections set, the Selleckchem FDA-Approved Drug Library (http://www.selleckchem.com/) and a selection of structurally diverse lead-like molecules selected from the BioAscent compound cloud (http://www.bioascent.com/compoundcloud/). Running this pilot screen provides useful data on the robustness of the assay over a normal screening day and provides an assessment of assay and target promiscuity in the form of the primary hit and confirmation rates. These data can then be used to inform the design of a screening cascade if the target is screened elsewhere, such as in the ELF. It is also a potential source of new hit compounds that the PO can exploit as chemical tools, reference molecules or starting points for drug development campaigns.

Knowledge exchange and student training

The SULSA-ADF creates an excellent opportunity for knowledge exchange and training for PhD students and postdoctoral researchers. This is presented as an offer to scientists from the POs' labs to work at the ESC Newhouse on their assay development project. We believe this maximises the chances of project success by acknowledging that the best person to develop a targeted assay is the person who has an in-depth practical experience of the biology underlying it. It also provides early career researchers with a good knowledge of this key aspect of drug discovery, in what amounts to an intensive residential training course. They can then take this new knowledge back to their home institutions and help incubate a culture of translational drug discovery, creating the potential for a virtuous cycle of new project submissions to the fund. In addition, young researchers will be better equipped either to exploit their own basic scientific discoveries if they remain in academia or will have extra skills to strengthen their CV if seeking employment in industry.

The availability of a scientist from a PO's lab to help with the assay development is established during the first project meeting, and plans are made for accommodating their stay at the ESC Newhouse. Unfortunately the fund does not cover living and travelling expenses, an obvious weakness of the current format. However, funding for this aspect of the project has always been met by the POs, who see the significant value of this training opportunity for students and staff. For example, in one Glasgow University project a knowledge exchange funding stream covered all of the costs associated with the placement.

Portfolio building, outcomes and impact

An immediate logistical requirement was to rapidly recruit a large enough number of project submissions to build a suitable portfolio. The scheme was devised as an open call to the community, in the hope of promoting a continual influx of molecular-target-based projects. However, project submissions were usually only forthcoming following an intense period of community engagement. Raising awareness among the six SULSA universities involved advertising on the SULSA website, direct email communication to the Technology Transfer Offices and researchers and, crucially, oral presentations and face-to-face networking. Networking proved to be the most productive approach, because direct discussions with academics helped establish the suitability of their project for the scheme and allowed an initial discussion on potential assay formats. More than 70% of project submissions were sourced through this approach.

Over the course of two years the project recruitment and assay development goals of the fund have been achieved (Table 1). Currently, 16 of 22 projects have been finished with 13 developed to ELF standards (Box 1). Of those failing to meet the ELF standards one cell-based project was completed but could not consistently obtain Z' values above 0.6 (a strict criteria within ELF), and two projects were halted at the feasibility stage because no suitable assay window was established. Six projects are still active. Of the 14 completed assays the median time from the initial planning meeting to completion of the assay development report was 8 weeks (Fig. 2). Most assays were completed in less than 12 weeks with three showing much longer timelines. These three assays encountered different delaying issues comprising: limited resourcing at the beginning of the SULSA-ADF; protein

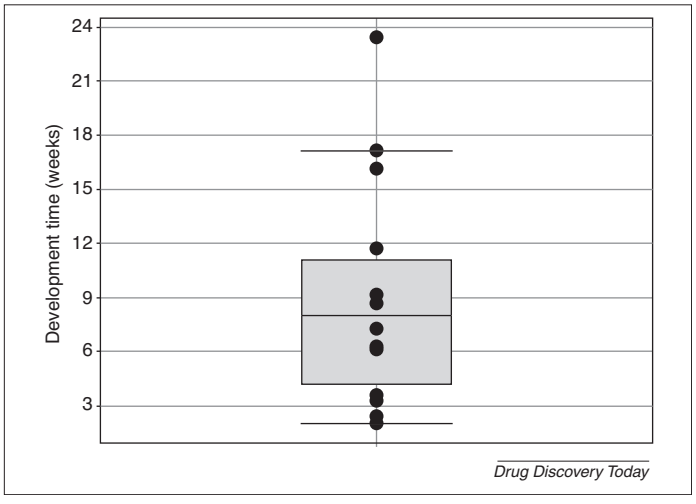

FIGURE 2

The time taken to development each assay meets the 8 week target for the majority of the projects, highlighting it as an efficient streamlined process for translation.

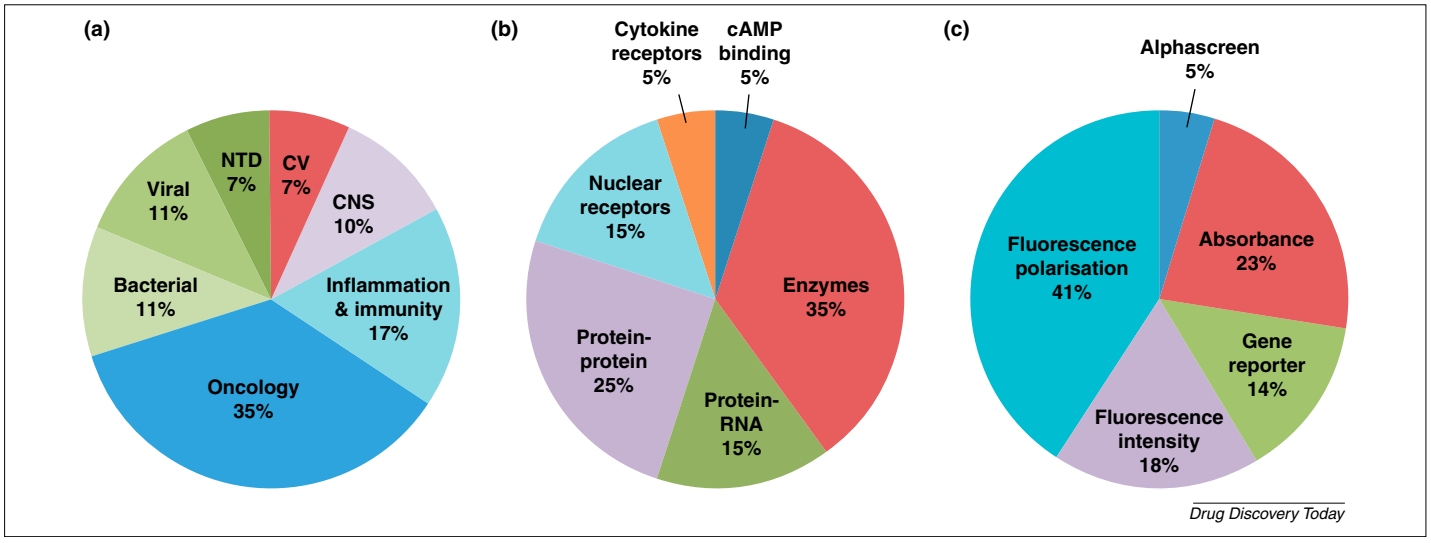

FIGURE 3

SULSA Assay Development Fund project portfolio overview detailing a % breakdown by **(a)** disease indication, **(b)** target class and **(c)** technology used to develop the assays. Abbreviations: CNS, central nervous system disease; CV, cardiovascular disease; NTD, neglected tropical disease.

production difficulties; and a cell line that required re-optimisation by the PO.

For the 13 projects meeting the ELF assay criteria, seven have been submitted to the ELF and all passed the technical check allowing them to be sent for scientific review. At the time of writing, five of these had been accepted into ELF with one awaiting review. Of the projects that met the ELF criteria, but were not submitted to ELF, one was not pursued further by the PO, one secured funding to run an HTS elsewhere and there are a further two submissions for ELF in preparation. With a mean cost per project at £13 600 and the cost of a large HTS and follow-up work within the ELF conservatively estimated at ~£500 000, successful submissions to the ELF clearly provide a significant return on investment. To date this is estimated to equate to an excess of £2.5 million and is likely to increase considerably as the portfolio is completed this year and the downstream benefits to the SULSA University POs are fully realised.

As planned, we created a diverse portfolio as can be seen when it is broken down by disease area, target class and screening technology adopted (Fig. 3). Of particular note, nearly one-third of the portfolio is focused on infectious diseases. Oncology represents the largest disease area and this probably reflects the research interests of the academic community. Examining the portfolio by target class there is a balance between more-difficult targets, such as protein–protein interactions (PPIs; 25%), protein–RNA interactions (PRIs; 15%) and cAMP-binding proteins (5%), and some traditionally more-druggable classes, such as enzymes (35%), nuclear receptors (15%) and cytokine receptors (5%). The large number of PPIs and PRIs has also skewed the assay technology towards fluorescence polarisation assays, predominantly because of the ease and cost efficiency of obtaining fluorescently labelled peptides and RNA. Notable by their absence are G-protein-coupled receptors (GPCRs) and ion channels, which could reflect reduced academic interest in this area or possibly indicate that assay development and screening for these targets is so mature that support from screening facilities is less in demand.

In total, six of the 16 completed projects in the portfolio were worked on by students and staff from the PO's lab-comprising three PhD students, one Master's student and two postdocs. The scheme attracted a very high calibre of individual. All of the students were in their final year and close to writing up their theses, ensuring they had a very high level of knowledge around their research projects, they were very technically adept in the lab and were highly motivated to complete the work in a timely manner. Mentoring of visiting-scientists was principally undertaken by the two ESC assay development scientists; although there was a time-penalty associated with training, this was typically no more than 2 weeks, at which point all involved were near self-sufficiency in the lab. Assessment of the benefit to these individuals from the scheme is somewhat qualitative but can be summed up in their own words (Box 2).

BOX 2

Quotes from Scottish Universities Life Sciences Alliance Assay Development Fund (SULSA-ADF) applicants and students.

'We only got so far in optimising our assay because in my opinion we do not have either the equipment or the personnel with the skill set required to do this efficiently. So being able to come and work at Newhouse where you are then surrounded by people who can identify quickly where assay improvements should be made and then pass on the knowledge of how to set about applying these changes (as well as gaining experience with various pieces of equipment) was invaluable.'

'The best aspect of the placement was the opportunity to translate molecular events to assays suitable for high throughput analysis and ultimately drug discovery. It is particularly satisfying to watch the basic molecular biology I studied during my PhD progress into the drug discovery process which may have real world application and is the first step towards a therapeutic agent.'

'Many of the jobs I have recently applied for include the development of molecular assays. With hands on experience in this process, my CV is certainly strengthened thanks to my time at Newhouse.'

Concluding remarks

The SULSA-ADF allows scientists from Scottish universities to unlock the translational potential of new biology, by providing avenues for significant follow-on funding leading to starting

points for new therapies that give real prospects for impacts on human health. Rather than directly providing grant-style funding to university academics, it has provided funds for ESC experts to enable the basic biology with specific assay development expertise tailored to an industry-perspective, and leveraged existing industry-grade facilities. The fund is meeting its predefined goals and has already demonstrated significant return on investment, shown by significant leveraged funding and the impact it is having on young researchers. It is fully expected that it will continue to deliver at the same level as it draws to completion. It has also resulted in academic opportunities for POs with at least three scientific publications detailing assay development and screening outcomes currently in preparation. Through this experience we believe it is crucial to provide academics with access to the necessary expertise and facilities that ensure their research can be useful and attractive to the pharma industry. By promoting this kind of catalytic activity, we are supporting collaborative efforts that engage all members of the scientific community, ensuring that all sectors contribute most efficiently towards improving human health.

Training young university scientists by transferring relevant translational knowledge into the academic community ensures that, over time, the gap between pharma and university life sciences research diminishes, and a more coherent and efficient framework for intersector collaboration emerges. We have also established that these kinds of schemes require the community to effect a culture change, manifest by the fact that only significant one-to-one networking prompted scientists to put their projects forward. We feel that this could be down to the unusual nature of the opportunity – no funds are directly gained by the academic – confounded with the necessity to make a small leap into the pharma mindset. However, the leap required is a small consideration compared with academics trying to achieve similar outcomes in-house, because we provide an existing facility to widen access and accelerate translational biology.

We strongly believe that there is a wealth of basic biology in academic life science departments that can contribute positively towards pharma's goals of finding new therapies but that unlocking this potential requires insight into academic work-ethic, dedicated industry-grade facilities and expertise, and specific pump-priming funding streams. With these elements in place it is possible to actively unlock the potential and remove the barriers that scientists are currently experiencing.

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